

II. AMENDMENTS TO CLAIMS

Claims 2-4, 10, 16-18, 24, 30-33 and 37, 38 were previously cancelled, without prejudice. Please add new claims 55-58, as set forth below.

IN THE CLAIMS:

1. *(Previously Presented)* A method for screening an individual for colorectal cancer, the method comprising determining the total concentration of TIMP-1 in a plasma sample of said individual, and indicating the individual as likely to have colorectal cancer if the total concentration of TIMP-1 is at or beyond a discriminating value and indicating the individual as unlikely to have colorectal cancer if the total concentration of TIMP-1 is not at or beyond the discriminating value, whereby the likelihood that said individual has or will have colorectal cancer is determined, the discriminating value being a value which has been determined by measuring the total concentration of TIMP-1 in both a healthy control population and a population with known colorectal cancer, thereby determining said discriminating value which identifies the colorectal cancer population with a predetermined sensitivity or predetermined specificity.

Claims 2-4, (Cancelled).

5. *(Previously Presented)* A method according to claim 41, wherein the combination is performed by logistic regression analysis.

6. *(Previously Presented)* A method according to claims 1 or 5, which comprises additionally determining at least one second parameter, the second

parameter representing the concentration of an additional tumour marker different from any form of TIMP-1, in a body fluid sample from the individual.

7. *(Previously Presented)* A method according to claim 6, wherein the total concentration of TIMP-1 in the plasma sample and the concentration of the additional tumour marker different from any form of TIMP-1 are combined to result in a combined parameter and indicating the individual as likely to have colorectal cancer if the combined parameter is at or beyond a discriminating value and indicating the individual as unlikely to have colorectal cancer if the combined parameter is not at or beyond the discriminating value.

8. *(Original)* A method according to claim 7, wherein the combining is performed by logistic regression analysis.

9. *(Previously Presented)* A method according to claim 7, wherein the discriminating value of the combined parameter is a value which has been determined by determining said combined parameter in both a healthy control population and a population with known colorectal cancer, thereby determining the discriminating value which identifies the colorectal cancer population with a predetermined specificity or a predetermined sensitivity.

Claim 10, (Cancelled).

11. *(Previously Presented)* A method according to claim 9, wherein the tumour marker is selected from the group consisting of CEA, soluble U-PAR, cathepsin B, HER2-neu, CA15-3 and YKL-40.

12. *(Original)* A method according to claim 11, wherein the at least one second parameter determined is the concentration of CEA.
13. *(Previously Presented)* A method according to claims 1, 41, 42 or 5, wherein the individual is a member of an unselected population.
14. *(Previously Presented)* A method according to claims 1, 41, 42 or 5, wherein the individual is a member of a population already identified as having an increased risk of developing cancer.
15. *(Previously Presented)* A method for screening an individual, who has been treated for primary breast cancer, for metastatic breast cancer, comprising determining the total concentration of TIMP-1 in a plasma sample of said individual, and indicating the individual as likely to have metastatic breast cancer if the total concentration of TIMP-1 is at or beyond a discriminating value and indicating the individual as unlikely to have metastatic breast cancer if the total concentration of TIMP-1 is not at or beyond the discriminating value, whereby the likelihood that said individual has or will have metastatic breast cancer is determined, the discriminating value being a value which has been determined by measuring the total concentration of TIMP-1 in both a healthy control population and a population with known metastatic breast cancer, thereby determining said discriminating value which identifies the metastatic breast cancer population with a predetermined sensitivity or a predetermined specificity.

Claims 16-18, (Cancelled)

19. *(Previously Presented)* A method according to claim 42, wherein the combination is performed by logistic regression analysis.

20. *(Previously Presented)* A method according to claims 15 or 19, which comprises additionally determining at least one second parameter, the second parameter representing the concentration of an additional tumour marker different from any form of TIMP-1, in a body fluid sample from the individual.

21. *(Previously Presented)* A method according to claim 20, wherein the total concentration of TIMP-1 in the plasma sample and the concentration of the additional tumour marker different from any form of TIMP-1 are combined to result in a combined parameter and indicating the individual as likely to have metastatic cancer if the combined parameter is at or beyond a discriminating value and indicating the individual as unlikely to have metastatic cancer if the combined parameter is not at or beyond the discriminating value.

22. *(Original)* A method according to claim 21, wherein the combining is performed by logistic regression analysis.

23. *(Original)* A method according to claim 21, wherein the discriminating value of the combined parameter is a value which has been determined by determining said combined parameter in both a healthy control population and a population with known metastatic cancer, thereby determining the discriminating value which identifies the metastatic cancer population with a predetermined specificity or a predetermined sensitivity.

Claim 24, (Cancelled).

25. *(Previously Presented)* A method according to claim 20, wherein the tumour marker is selected from the group consisting of CEA, soluble u-PAR, cathepsin B, HER2-neu, CA15-3 and YKL-40.

26. *(Original)* A method according to claim 25, wherein the at least one second parameter determined is the concentration of CEA.

27. *(Previously Presented)* A method according to claim 15, wherein the determination is performed at several time points at intervals as part of a monitoring of a cancer patient after the treatment for primary breast cancer.

28. *(Previously Presented)* A method according to claim 1, which detects early stage cancer.

29. *(Original)* A method according to claim 28, wherein the early stage cancer is selected from the group consisting of colon cancer Dukes' stage A, colon cancer Dukes' stage B, colon cancer Dukes' stage C, rectal cancer Dukes' stage A, rectal cancer Dukes' stage B and rectal cancer Dukes' stage C.

Claims 30-33, (Cancelled).

34. *(Previously Presented)* A method according to claims 1 or 15, wherein the total concentration of TIMP-1 is performed by means of an immuno assay or an activity assay.

35. *(Original)* A method according to claim 34, wherein the immuno assay is an ELISA.

36. *(Original)* A method according to claim 34, wherein the activity assay is zymography.

Claim 37-38, (Cancelled).

39. *(Previously Presented)* A method according to claim 1 wherein the colorectal cancer is colon cancer.

40. *(Previously Presented)* A method according to claim 1 wherein the colorectal cancer is rectal cancer.

41. *(Previously Presented)* A method for screening an individual for colorectal cancer, the method comprising determining the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 in a plasma sample of said individual, and indicating the individual as likely to have colorectal cancer if the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 is at or beyond a discriminating value and indicating the individual as unlikely to have colorectal cancer if the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 is not at or beyond the discriminating value, whereby the likelihood that said individual has or will have colorectal cancer is determined, the discriminating value being a value which has been determined by measuring the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 in both a healthy control population and a population with known colorectal cancer, thereby determining

said discriminating value which identifies the colorectal cancer population with a predetermined sensitivity or a predetermined specificity.

42. *(Previously Presented)* A method for screening an individual, who has been treated for primary breast cancer, for metastatic breast cancer, the method comprising determining the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 in a plasma sample of said individual, and indicating the individual as likely to have metastatic breast cancer if the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 is at or beyond a discriminating value and indicating the individual as unlikely to have metastatic breast cancer if the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 is not at or beyond the discriminating value, whereby the likelihood that said individual has or will have metastatic breast cancer is determined, the discriminating value being a value which has been determined by measuring the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 in both a healthy control population and a population with known metastatic breast cancer, thereby determining said discriminating value which identifies the metastatic breast cancer population with a predetermined sensitivity or a predetermined specificity.

43. *(Previously Presented)* A method according to claim 6, wherein the additional tumour marker is a colorectal tumour marker.

44. *(Previously Presented)* A method according to claim 43, wherein the total concentration of TIMP-1 in the plasma sample and the concentration of the additional tumour marker different from any form of TIMP-1 are combined to result in a combined

parameter and indicating the individual as likely to have colorectal cancer if the combined parameter is at or beyond a discriminating value and indicating the individual as unlikely to have colorectal cancer if the combined parameter is not at or beyond the discriminating value.

45. *(Previously Presented)* A method according to claim 44, wherein the combining is performed by logistic regression analysis.

46. *(Previously Presented)* A method according to claim 44, wherein the discriminating value of the combined parameter is a value which has been determined by determining said combined parameter in both a healthy control population and a population with known colorectal cancer, thereby determining the discriminating value which identifies the colorectal cancer population with a predetermined specificity or a predetermined sensitivity.

47. *(Previously Presented)* A method according to claim 46, wherein the tumour marker is selected from the group consisting of CEA, soluble U-PAR, cathepsin B, HER2-neu, CA15-3 and YKL-40.

48. *(Previously Presented)* A method according to claim 47, wherein the at least one second parameter determined is the concentration of CEA.

49. *(Previously Presented)* A method according to claim 43, wherein the individual is a member of an unselected population.

50. *(Previously Presented)* A method according to claim 43, wherein the individual is a member of a population already identified as having an increased risk of developing cancer.

51. *(New)* A method according to claim 14, wherein the individual has a genetic disposition for cancer, has been exposed to carcinogenic substances or has a cancer-predisposing or non-malignant diseases.

52. *(New)* A method according to claim 14, wherein the individual is selected from the group consisting of: an individual who had a prior polyp, an individual with Crohn's disease, an individual with an ulcerative colitis, an individual with one or more family members with colorectal cancer, or an individual with a prior resection of early colorectal cancer.

53. *(New)* A method according to claim 50, wherein the individual has a genetic disposition for cancer, has been exposed to carcinogenic substances or has a cancer-predisposing or non-malignant diseases.

54. *(New)* A method according to claim 50, wherein the individual is selected from the group consisting of: an individual who had a prior polyp, an individual with Crohn's disease, an individual with an ulcerative colitis, an individual with one or more family members with colorectal cancer, or an individual with a resection of early colorectal cancer.